

# sinemet\*

(levodopa and carbidopa combination)

## INDICATIONS

Treatment of Parkinson's syndrome with exception of drug induced parkinsonism.

## CONTRAINDICATIONS

When a sympathomimetic amine is contraindicated; with monoamine oxidase inhibitors, which should be discontinued two weeks prior to starting SINEMET\*; in uncompensated cardiovascular, endocrine, hematologic, hepatic, pulmonary or renal disease; in narrow-angle glaucoma; in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

## WARNINGS

When given to patients receiving levodopa alone, discontinue levodopa at least 12 hours before initiating SINEMET\* at a dosage that provides approximately 20% of previous levodopa.

Not recommended in drug-induced extrapyramidal reactions; contraindicated in management of intention tremor and Huntington's chorea.

Levodopa related central effects such as involuntary movements may occur at lower dosages and sooner, and the 'on and off' phenomenon may appear earlier with combination therapy.

Monitor carefully all patients for the development of mental changes, depression with suicidal tendencies, or other serious antisocial behaviour.

Cardiac function should be monitored continuously during period of initial dosage adjustment in patients with arrhythmias.

Safety of SINEMET\* in patients under 18 years of age not established.

**Pregnancy and lactation:** In women of child-bearing potential, weigh benefits against risks. Should not be given to nursing mothers. Effects on human pregnancy and lactation unknown.

## PRECAUTIONS

**General:** Periodic evaluations of hepatic, hematopoietic, cardiovascular and renal function recommended in extended therapy. Treat patients with history of convulsions cautiously. **Physical Activity:** Advise patients improved on SINEMET\* to increase physical activities gradually, with caution consistent with other medical considerations. **In Glaucoma:** May be given cautiously to patients with wide angle glaucoma, provided intraocular pressure is well controlled and can be carefully monitored during therapy. **With Anti-hypertensive Therapy:** Asymptomatic postural hypotension has been reported occasionally, give cautiously to patients on antihypertensive drugs, checking carefully for changes in pulse rate and blood pressure. Dosage adjustment of antihypertensive drug may be required. **With Psychoactive Drugs:** If concomitant administration is necessary, administer psychoactive drugs with great caution and observe patients for unusual adverse reactions. **With Anesthetics:** Discontinue SINEMET\* the night before general anesthesia and reinstitute as soon as patient can take medication orally.

## ADVERSE REACTIONS

**Most Common:** Abnormal Involuntary Movements—usually diminished by dosage reduction—choreiform, dystonic and other involuntary movements. Muscle twitching and blepharospasm may be early signs of excessive dosage. **Other Serious Reactions:** Oscillations in performance: diurnal variations, independent oscillations in akinesia with stereotyped dyskinesias, sudden akinetic crises related to dyskinesias, akinesia paradoxa (hypotonic freezing) and 'on and off' phenomenon. **Psychiatric:** paranoid ideation, psychotic episodes, depression with or without development of suicidal tendencies and dementia. Rarely convulsions (causal relationship not established). Cardiac irregularities and/or palpitations, orthostatic hypotensive episodes, anorexia, nausea, vomiting and dizziness.

## Other adverse reactions that may occur:

**Psychiatric:** increased libido with serious antisocial behavior, euphoria, lethargy, sedation, stimulation, fatigue and malaise, confusion, insomnia, nightmares, hallucinations and delusions, agitation and anxiety. **Neurologic:** ataxia, faintness, impairment of gait, headache, increased hand tremor, akinetic episodes, 'akinesia paradoxa', increase in the frequency and duration of the oscillations in performance, torticollis, trismus, tightness of the mouth, lips or tongue, oculogyric crisis, weakness, numbness, bruxism, priapism. **Gastrointestinal:** constipation, diarrhea, epigastric and abdominal distress and pain, flatulence; eructation, hiccups, sialorrhea; difficulty in swallowing, bitter taste, dry mouth; duodenal ulcer; gastrointestinal bleeding; burning sensation of the tongue. **Cardiovascular:** arrhythmias, hypotension, non-specific ECG changes, flushing, phlebitis. **Hematologic:** hemolytic anemia, leukopenia, agranulocytosis. **Dermatologic:** sweating, edema, hair loss, pallor, rash, bad odor, dark sweat. **Musculoskeletal:** low back pain, muscle spasm and twitching, musculoskeletal pain. **Respiratory:** feeling of pressure in the chest, cough, hoarseness, bizarre breathing pattern, postnasal drip. **Urogenital:** urinary frequency, retention, incontinence, hematuria, dark urine, nocturia, and one report of interstitial nephritis. **Special Senses:** blurred vision, diplopia, dilated pupils, activation of latent Horner's syndrome. **Miscellaneous:** hot flashes, weight gain or loss. Abnormalities in laboratory tests reported with levodopa alone, which may occur with SINEMET\*: Elevations of blood urea nitrogen, SGOT, SGPT, LDH, bilirubin, alkaline phosphatase or protein bound iodine. Occasional reduction in WBC, hemoglobin and hematocrit. Elevations of uric acid with colorimetric method. Positive Coombs tests reported both with SINEMET\* and with levodopa alone, but hemolytic anemia extremely rare.

## DOSAGE SUMMARY

*In order to reduce the incidence of adverse reactions and achieve maximal benefit, therapy with SINEMET\* must be individualized and drug administration continuously matched to the needs and tolerance of the patient. Combined therapy with SINEMET\* has a narrower therapeutic range than with levodopa alone because of its greater milligram potency. Therefore, titration and adjustment of dosage should be made in small steps and recommended dosage ranges not be exceeded. Appearance of involuntary movements should be regarded as a sign of levodopa toxicity and an indication of overdosage, requiring dose reduction. Treatment should, therefore, aim at maximal benefit without dyskinesias.*

### Therapy in Patients not receiving Levodopa:

Initially ½ tablet once or twice a day, increase by ½ tablet every three days if desirable. An optimum dose of 3 to 5 tablets a day divided into 4 to 6 doses.

### Therapy in Patients receiving Levodopa:

Discontinue levodopa for at least 12 hours, then give approximately 20% of the previous levodopa dose in 4 to 6 divided doses.

FOR COMPLETE PRESCRIBING INFORMATION, PARTICULARLY DETAILS OF DOSAGE AND ADMINISTRATION, PLEASE CONSULT PRODUCT MONOGRAPH WHICH IS AVAILABLE ON REQUEST.

## HOW SUPPLIED

Ca 8804—Tablets SINEMET\* 250, dapple-blue, oval, biconvex, scored, compressed tablets coded MSD 654, each containing 25 mg of carbidopa and 250 mg of levodopa. Available in bottles of 100.



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(SNM-7-487-JA)

## Arteriovenous malformation of the jejunum

*To the editor:* Three years ago we treated a patient with an arteriovenous malformation as described in the following case report.

A 73-year-old man was admitted to hospital with weakness, dizziness and a decrease in hemoglobin concentration that had been detected in his family physician's office over the previous 3 weeks. He had no melena or change in stool colour, and no pain, nausea, vomiting or other symptoms.

The patient had a 25-year history of painless intermittent melena and anemia requiring transfusion "about 50 times". His only previous operations were two hemorrhoidectomies — one 20 years ago and another 4 years ago. The second had been preceded by full work-up for gastrointestinal tract bleeding. In recent years, on numerous admissions to several local hospitals, repeated investigation had been done by gastroenterologists and hematologists. No clues were found to the cause of his low hemoglobin concentration other than iron-deficiency anemia, and no therapy other than multiple transfusions and iron pills was given. His hemoglobin concentration would decrease to as low as 5.2 g/dL.

He appeared well developed and well nourished and was in no distress. The findings on physical examination, which included rectal examination, were normal; blood pressure was 150/75 mm Hg; pulse rate, 100 beats/min with a regular rhythm; and respiratory rate, 24/min. Hemoglobin concentration was 8.6 g/dL and hematocrit, 28%.

Since numerous barium radiographic studies and endoscopies had failed to disclose the diagnosis, selective superior mesenteric arteriography was performed. A dilated third jejunal artery — a branch of the superior mesenteric artery — led into multiple irregular vascular channels within the bowel wall; at this point early filling of a large jejunal vein was seen at the same level, extending over an 8- to 9-cm segment of jejunum.

At laparotomy a 70-cm length of the wall of the jejunum was found to be thickened and to contain large pulsating vessels. This portion was resected and an end-to-end anastomosis performed 10 cm distal to the ligament of Treitz. Pathologic examination revealed a thickened, congested jejunal wall with large arteries and veins in the submucosa but without edema or inflammation; no specific microanatomic vascular lesion was seen.

The patient's recovery was uneventful. In the 3 years since operation there has been no recurrence of anemia or bleeding.

The source of massive alimentary tract hemorrhage is usually confirmed by conventional methods such as barium studies and endoscopy. However, many patients with bleeding from the upper gastrointestinal tract will be discharged from hospital without a diagnosis. In a series of 1000 cases analysed

## Summary of prescribing information:

**Pharmacology:** Spironolactone effects diuresis by blocking through competitive inhibition, the sodium and water retaining and potassium excreting effects of aldosterone on the distal renal tubule. Hydrochlorothiazide promotes excretion of sodium and water primarily by inhibiting their reabsorption by the cortical diluting segment of the renal tubule. Thus the components of Aldactazide have different and complementary modes of action. In addition, spironolactone minimizes potassium loss characteristically induced by hydrochlorothiazide, thereby reducing the possible serious consequences of potassium depletion.

**Indications:** The treatment of essential hypertension; the edema and ascites of congestive heart failure, cirrhosis of the liver, the nephrotic syndrome and idiopathic edema.

**Contraindications:** Acute renal insufficiency; rapidly progressing impairment of renal function; anuria; hyperkalemia; patients known to be sensitive to thiazides or other sulfonamide-derived drugs; patients with severe or progressive liver disease at the discretion of the physician; nursing mothers; sensitivity to spironolactone.

**Warnings:** Concurrent potassium supplementation is not indicated unless a glucocorticoid is also given. Aldactazide should not be used in conjunction with other potassium conserving agents.

**Precautions:** The most potentially serious electrolyte disturbance is hyperkalemia which is more likely to occur in severely ill patients. If hyperkalemia occurs, discontinue Aldactazide. Hypokalemia may develop. Use cautiously in patients with sodium depletion. Check for signs of fluid or electrolyte imbalance. The most frequent electrolyte disturbance encountered is dilutional hyponatremia. Rarely a true low-salt syndrome may develop. Decrease dosage before diuresis is complete to avoid dehydration. Thiazide diuretics may precipitate hepatic coma. Use with caution in patients subjected to regional or general anesthesia. Discontinue 48 hours prior to elective surgery as both hydrochlorothiazide and spironolactone reduce vascular responsiveness to norepinephrine. Orthostatic hypotension may occur. Thiazides may increase responsiveness to tubocurarine. Pathological changes in the parathyroid glands have been observed. Consider the possibilities of sensitivity reactions in patients with a history of allergy or asthma as well as exacerbation of systemic lupus erythematosus. Thiazides may cause elevation of BUN. Aldactazide may potentiate the effect of other antihypertensives especially the ganglionic blocking agents. The dosage of such drugs should be reduced at least 50% when Aldactazide is added to the regimen. Spironolactone interferes with the assay of plasma cortisol but not the Ertel method. ASA may interfere with the action of spironolactone. Use with caution in patients with hyperuricemia or history of gout. Insulin requirements may be increased, decreased or unchanged in diabetics. Hyperglycemia and glycosuria may be manifested in latent diabetics. Use with caution in women of child-bearing age and weigh benefits against the possible hazards to the fetus.

**Adverse Effects:** Nausea or other gastrointestinal disturbances, gynecomastia or mild androgenic manifestations have been reported in some patients. Other side effects including those of hydrochlorothiazide occur less frequently.

**Overdose:** Symptoms of Overdose: Acute overdose may be manifested by drowsiness, mental confusion, maculopapular or erythematous rash, nausea, vomiting, dizziness or diarrhea. Rare instances of hypokalemia, hyponatremia, hyperkalemia or hepatic coma may occur. Thrombocytopenic purpura and granulocytopenia have occurred with thiazide therapy. No specific antidote. Treat fluid depletion and electrolyte imbalances as indicated.

**Dosage:** In essential hypertension, a daily dosage of 2 to 4 tablets, in divided doses, will be adequate for most patients, provided the treatment is continued for 2 weeks or longer. Dosage may range from 2 to 8 tablets daily. Dosage should be adjusted according to the response of the patient.

In edematous states, a daily dosage of 2 to 4 tablets, in divided doses, will be adequate for most patients but may range from 2 to 8 tablets daily. Dosage should be adjusted according to the response of the patient.

**Supply:** Each round, ivory-coloured tablet contains, spironolactone, 25 mg and hydrochlorothiazide, 25 mg. Available in bottles of 100, 1,000 and 2,500 tablets.

Complete prescribing information available on request

SEARLE

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by Palmer<sup>1</sup> the cause of the bleeding could not be discovered in 8%.

Since the introduction of angiography successful diagnosis of arteriovenous malformation of the bowel has been reported from time to time. Most of the malformations have been in the cecum and ascending colon, being fed by either the ileocolic or the right colic artery. In the Dartmouth study,<sup>2</sup> in which angiography was used in 22 patients with intestinal hemorrhage undiagnosed by barium contrast radiography, endoscopy or laparotomy, four such malformations were found, all in the cecum.

Of the 17 reported cases of angiographically diagnosed arteriovenous malformation in the bowel only 2 had jejunal malformations. The first was reported in 1968 in a 46-year-old woman with an 18-year history of intermittent melena.<sup>3</sup> In 1970 a 65-year-old man with a 10-year history of melena was treated at the Mayo Clinic; the jejunal arteriovenous malformation was angiographically demonstrated.<sup>4</sup> Both patients had had laparotomies without relief. Their histories were similar to that of our patient and seemed to be typical of the way in which these cases present.

Angiography is therefore an important diagnostic aid in the investigation of obscure bleeding from the gastrointestinal tract.

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## Prostaglandins and the ductus arteriosus

To the editor: The editorial by E.M. Cooperman (*Can Med Assoc J* 117: 309, 1977) has drawn attention to the exciting new developments in our understanding of the role of prostaglandins in the regulation of ductus arteriosus closure. Yet, as so often happens, credit was not given to the Canadian investigators who have undertaken the work in this field. The work of Olley, Coceani and Bodach<sup>1</sup> was cited, but nowhere in the article could someone

unaware of the story discover that the team that did much of the basic research and pioneered the clinical use of prostaglandins in children is based in Toronto. Surely this information ought to be of interest to readers of the *Journal*.

Cooperman failed to point out that, as a result of the Toronto group's findings of the importance of prostaglandins in maintaining patency of the ductus, two different approaches to the problem of the patent ductus were simultaneously and independently developed. The approach Cooperman mentioned — inhibition of prostaglandin synthesis by indomethacin and acetylsalicylic acid — was tried in the United States. In Canada it was found, on the basis of laboratory research, that the antimalarial chloroquine was an antagonist of prostaglandin action rather than an inhibitor of prostaglandin synthesis.<sup>2</sup> Because chloroquine has a record of safe use in neonatal malaria, Collins and colleagues,<sup>3</sup> at the Montreal Children's Hospital, tested it in infants with the patent ductus syndrome and obtained encouraging results. The use of indomethacin obviously causes problems and I believe that chloroquine may prove to be the better drug. The use of chloroquine was reported by me and my colleagues in your sister weekly journals — the *Journal of the American Medical Association*<sup>4</sup> and the *Lancet*.<sup>5</sup> It is unfortunate that the *CMA Journal* should pay more attention to the work being carried out in the United States than that being carried out in Toronto and Montreal.

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## Chronic active hepatitis in a child with hemophilia A

To the editor: Hepatitis is a major complication of blood transfusion therapy, and the use of fractions prepared from large plasma pools has increased the risk. Both Factor VIII and Factor IX concentrates can be implicated as possible sources of the virus.<sup>1-5</sup> In view of this, one would expect to find antibody